

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S,

Plaintiff,

v.

C.A. No. 05-160-KAJ

GENENCOR INTERNATIONAL, INC. and
ENZYME DEVELOPMENT CORPORATION,

Defendants.

DEFENDANTS' OPENING POST-TRIAL BRIEF

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I. INTRODUCTION

The evidence at trial demonstrated clearly that Machius '95 renders obvious Novozymes' U.S. Patent No. 6,867,031 (the "'031 Patent"). Machius '95 provides highly material information that would have motivated an ordinarily skilled protein engineer to make the Suzuki 179-180 deletion in BSG, more motivation even than provided by Suzuki itself. Reading Machius '95, a protein engineer would have such a high expectation of success that making the Suzuki deletion in BSG would be considered a "no-brainer." Novozymes, including attorney Jason Garbell and inventor Torben Borchert, were very familiar with Machius '95 and knew of its materiality to the '031 Patent. Novozymes intentionally withheld Machius '95 from the Examiner, driven to obtain the '031 Patent by the success of Genencor's SPEZYME® Ethyl.

Novozymes had little choice but to conceal Machius '95 if it wanted the '031 Patent to issue. After the Examiner had earlier rejected claims based on Suzuki and the Bisgard-Frantzen PCT, Novozymes could not risk disclosure of the even stronger prior art of Machius '95. So, Novozymes withheld Machius '95 from the Examiner, and hatched a plan to "overcome" Suzuki. The plan was to offer narrowed claims in order to "buy time" to perform allegedly comparative experiments (vs. Suzuki), after which Novozymes would take back those "straw man" narrowed claims and obtain broad claims to use against Genencor and EDC (collectively "Genencor").

The key element in Novozymes' plan was the Borchert Declaration, which provided the "results" of an alleged experiment comparing relative improvement in thermostability of two enzymes after making the 179-180 deletion taught by Suzuki. Even though Mr. Garbell expressly designed the test to compare to Suzuki's results on thermostability, the Borchert experiment was different from Suzuki in critical respects. Not surprisingly, the differences from Suzuki helped Novozymes' argument for patentability.

What is more, Novozymes failed to present numerous data points from the "experiment" (even though Mr. Garbell claimed to have given instructions that all results should be reported), improperly extrapolated a half-life for BSG del, and failed to account for the effect of "ramp-up"

time in heating the short-lived BAN WT. As a result, the Borchert Declaration did not fairly compare to Suzuki, and presented an unreliable, overstated improvement in BSG against an artificially lowered improvement in BAN. The “true” relative improvement was approximately 2-fold, in the same range as Suzuki and not unexpected at all.

The Examiner allowed the asserted claims of the '031 Patent as a direct result of Novozymes' intentional misrepresentations regarding the “very surprising” and “unexpected” nature of the results, and the intentional nondisclosure of Machius '95. Even then, Novozymes had the chance to do the right thing regarding Machius '95—pulling the '031 Patent from issuance so that the most material prior art could be disclosed and the issue of obviousness decided in the U.S. Patent Office (“PTO”) during prosecution (rather than litigation).

But Novozymes did not take that step. Why? Because Novozymes needed some way to attack Genencor's SPEZYME® Ethyl, which had better performance and a lower price than Novozymes' highly profitable Liquozyme SC. And, as Mr. Garbell candidly admitted, the '031 Patent might not have issued had Novozymes disclosed Machius '95 and allowed the Examiner to do her job.

The '031 Patent should never have issued, and this case should never had been brought. Genencor is entitled to judgment, on many grounds.

II. **GENENCOR IS ENTITLED TO JUDGMENT OF NON-INFRINGEMENT, INVALIDITY, AND UNENFORCEABILITY**

A. **Non-Infringement**

This Court should enter judgment for Genencor because Novozymes has not met its burden to prove that SPEZYME® Ethyl literally infringes any of asserted claims 1, 3, and 5 of the '031 Patent.

First, whether the Court construes the term “*Bacillus stearothermophilus* alpha-amylase” to mean either: (i) “an alpha-amylase having the amino acid sequence of SEQ ID NO:3” or (ii) “a 514 or 515 amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase

gene, minus the signal sequence,” SPEZYME® Ethyl does not infringe claims 1 or 3 because the % homology between the amino acid sequences of SPEZYME® Ethyl and either SEQ ID NO:3 or a properly defined “*Bacillus stearothermophilus* alpha-amylase,” using a method that counts all deletions, is always less than 95%.

Second, even if the Court determines that the relevant “parent” or “*Bacillus stearothermophilus* alpha-amylase” is “the” alpha-amylase protein of G-ZYME® G997, Novozymes cannot meet its burden of proof because the amino acid sequence of G-ZYME® G997 is uncertain and variable, and is, therefore, a legally impermissible baseline against which to compare an accused product.

Third, SPEZYME® Ethyl does not infringe claim 5, because SPEZYME® Ethyl contains changes from its parent (the alpha-amylase encoded by the gene of strain G997) in addition to the two deletions to which claim 5 is limited by virtue of its “consists of” transitional phase.

B. Invalidity

This Court should enter judgment for Genencor because the '031 Patent is invalid as obvious and non-enabled.

The case for obviousness is overwhelming. Novozymes has admitted time and again that Suzuki and the Bisgard-Frantzen PCT render obvious the '031 Patent. The unreliable, misleading Borchert Declaration fails to present truly “unexpected results,” different “in kind” from Suzuki and sufficient to overcome the admitted obviousness of the '031 Patent. Those supposed “unexpected results” are even less of a response to Machius '95, which teaches more than Suzuki and which was not provided or cited to the Examiner during prosecution of the '031 Patent.

Claims 1 and 3 of the '031 Patent are also invalid because the '031 Patent does not provide sufficient disclosure to enable a protein engineer to make the variants of claims 1 and 3 without undue experimentation. The '031 Patent provides no meaningful guidance as to which sequence changes in a parent *Bacillus stearothermophilus* alpha-amylase, other than a handful, will lead to proteins that are at least 95% homologous to SEQ ID NO:3, contain the required

deletion, and have alpha-amylase activity. A skilled protein engineer would need to conduct thousands of millions of assays and experiments and select from an astronomically large number of possible variants to find even a small fraction of the claimed variants.

C. **Unenforceability**

This Court should enter judgment for Genencor because the '031 Patent is unenforceable due to inequitable conduct.

Novozymes' Dr. Borchert and Mr. Garbell failed to disclose Machius '95 to the PTO during the prosecution of the '031 Patent, even though they knew that Machius '95 provides relevant, highly material information not found in Suzuki. Dr. Borchert and Mr. Garbell also made numerous misrepresentations in and regarding the Borchert Declaration and underlying experiment. Novozymes had substantial, contemporaneous commercial motivation, caused by significant sales of SPEZYME® Ethyl and lost sales of Novozymes' Liquozyme SC, to manipulate the patent process in order to obtain issuance of the '031 Patent. This motivation led Novozymes to act with deceptive intent in withholding Machius '95 and in filing the improper Borchert Declaration.

III. SPEZYME® ETHYL DOES NOT LITERALLY INFRINGE ASSERTED CLAIMS 1, 3, AND 5 OF THE '031 PATENT

A. **Novozymes Bears the Burden of Proving Literal Infringement**

Novozymes bears the burden of proving literal infringement by a preponderance of the evidence. *See Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1364 (Fed. Cir. 2000). Determining patent infringement involves two basic steps: properly construing the claims to determine their meaning and scope, which is a question of law, and comparing the properly construed claims with the accused product to determine if there is infringement, which is a question of fact. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). (CL 1.) Once the claim terms are construed, literal infringement is found only when each and every element set forth in the patent claim is found in the accused

product. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed. Cir. 1995). (CL 8.)¹

B. Claim Construction

(1) Summary of the Legal Standard

Claim terms are generally given their ordinary and customary meaning, as understood by one of ordinary skill in the art at the time of the invention when read in view of the patent specification and prosecution. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13, 1321 (Fed. Cir. 2005), *cert. denied*, 126 S. Ct. 1332 (2006); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The Federal Circuit has specifically cautioned against placing too much emphasis on the alleged “ordinary meaning” of a term outside the context of the specification. *See Curtiss-Wright Flow Corp. v. Velan, Inc.*, 438 F.3d 1374, 1378-79 (Fed. Cir. 2006). The prosecution history also can inform the meaning of claim language by demonstrating how the inventor defined and/or limited the scope of the claims during the course of prosecution to obtain claim allowance. *See, e.g., Phillips*, 415 F.3d at 1317; *Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1579-80 (Fed. Cir. 1996). (CL 2-8.)

(2) Genencor’s Construction – “Parent *Bacillus stearothermophilus* Alpha-amylase” Means “SEQ ID NO:3”

The term “parent *Bacillus stearothermophilus* alpha-amylase” in claims 1 and 5 should be construed to mean “an alpha-amylase having the amino acid sequence of SEQ ID NO:3.” While the ’031 Patent specification provides several broad alternative definitions of differing

¹ The Court is by now familiar with the factual background of this case, which is repeated here only as necessary to give context to particular arguments. The Proposed Findings of Fact and Conclusions of Law sets forth all of the relevant evidence and law, and is generally cited as “FF ___” (for proposed findings of fact) or “CL ___” (for proposed conclusions of law). In addition, key trial evidence is often directly cited, by reference to “TE” (trial exhibits), “Tr.” (the trial transcript), or “A-” (the parties’ Joint Appendix).

scope, the one most consistent with the prosecution of the '031 Patent is "an alpha-amylase with the amino acid sequence of SEQ ID NO:3."² (FF 135; CL 12.)

In this case, the Examiner advanced and relied upon the definition for "parent" that Genencor maintains is correct, *i.e.*, that "parent" is a protein having the amino acid sequence of SEQ ID NO:3.³ During prosecution, Novozymes initially presented claims that defined the parent alpha-amylase as having a certain percent homology to SEQ ID NO:3, and not reciting any percent homology between the parent and the variant. (TE 101 at 5-7, A-7045-7047.) The Examiner rejected those claims under 35 U.S.C. § 112 as lacking written description and enablement in an Office Action ("OA") dated July 29, 2003. The Examiner stated that the rejection could be overcome by specifying that the variant alpha-amylase had a certain percent homology to "SEQ ID NO:3." (TE 101 at 583-87, A-7623-7627 (emphasis added.)) In response, Novozymes amended the claims but did not follow the Examiner's suggestion, choosing instead to amend the claims to require that the variant have a certain percent homology to its "parent." (TE 101 at 594-95, A-7634-7635.) (FF 136-138; CL 12.)

In an OA mailed April 6, 2004, the Examiner again rejected all of these claims under 35 U.S.C. § 112 as too broad, stating, *inter alia*, that the specification did not enable a variant that is at least 80% identical to a parent that is at least 80% to 95% identical to "SEQ ID NO:3." According to the Examiner, the pending claims encompassed alpha-amylases with an enormous number of variations not enabled by the few examples in the specification. But, the Examiner said, the specification did enable variant alpha-amylases having at least 90% homology to SEQ ID NO:3. Thus, the Examiner stated that the variant should be defined by its percent homology

² A timeline of the '031 Patent prosecution is provided at Appendix A.

³ When faced with multiple definitions of a claim term in a patent, the Federal Circuit has held that the definition relied upon by the Examiner in allowing the claims should be chosen, and definitions which the Examiner could not reasonably have relied upon should be rejected. *See Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1564-65 (Fed. Cir. 1994). (CL 3.)

to SEQ ID NO:3, and not to a “parent,” which was too broad. (TE 101 at 679-86, A-7719-7726.) (FF 139.)

In response, in the September 6, 2004 amendment, Novozymes canceled all claims and added new claims, which issued as claims 1-5 of the '031 Patent. New claim 48, which issued as claim 1, recited a “variant” that has 95% homology to the “parent,” without specifying any degree of homology between the parent and SEQ ID NO:3. Novozymes’ statements, especially read against the Examiner’s comments, however, clearly defined “parent” as SEQ ID NO:3. (FF 140.)

Specifically, in setting out the support for the new claims, Novozymes cited to the third and fifth paragraphs on page 10 of the specification, which Novozymes characterized in the amendment as “describing variants of *Bacillus stearothermophilus* and variants having at least 95% homology to SEQ ID NO:3” (emphasis added). The passages cited by Novozymes corresponding to the '031 Patent, 7:32-35 and 7:41-51 (TE 100 at 11 cols. 7:32-35, 7:41-51, A-7011), refer only to SEQ ID NO:3 and not to any other or broader definition of “parent.” (TE 101 at 694-695, A-7734-7735.) In addition, Novozymes asserted that the new claims comported with the Examiner’s suggestion to define the variants with respect to SEQ ID NO:3. In the September 6, 2004 amendment, Novozymes stated:

The Office concluded that although these [previous] claims are enabled for alpha-amylase variants having 90% homology to SEQ ID NO:3, that [sic] these claims lack enablement for alpha-amylase variants having 80% or 85% homology to SEQ ID NO. 3.

Applicants respectfully submit that this rejection is rendered moot by the new claims as the new claims recite a homology of 95%.

(TE 101 at 695-696, A-7735-7736 (emphasis added.)) Further, Novozymes explicitly stated that “[t]he presently claimed invention is directed to variants of *Bacillus stearothermophilus* alpha-amylase enzymes and to alpha-amylase variants having 95% homology to SEQ ID NO:3.” (TE 101 at 696, A-7736 (emphasis added.)) (FF 140-142.)

In order to convince the Examiner that the new claims overcame the Examiner's rejections of the prior claims, Novozymes stated that the *Bacillus stearothermophilus* alpha-amylase of what is now claim 1 is "SEQ ID NO:3." It is axiomatic that Novozymes cannot advance a narrow definition during prosecution to secure claim allowance and then advance a broader definition to encompass alleged infringers. *See Southwall Techs.*, 54 F.3d at 1576. Novozymes must, as a matter of law, maintain the same construction for "parent" it used to induce the Examiner to allow the claims during prosecution. Otherwise, Novozymes would be broadening the meaning of a claim term contrary to the intrinsic record, "which violates the principles articulated in *Phillips*." *Nystrom v. TREX Co.*, 424 F.3d 1136, 1145-46 (Fed. Cir. 2005). (CL 4-6.)

While Novozymes is expected to object that this construction of "parent" yields the result that independent claims 1 and 3 are of essentially the same scope, here the specification and prosecution history of the '031 Patent compels the conclusion that "SEQ ID NO:3" is the only appropriate definition of "*Bacillus stearothermophilus* alpha-amylase." Novozymes' clear statements in prosecution overcome any presumption of claim differentiation. *See Kraft Foods, Inc. v. International Trading Co.*, 203 F.3d 1362, 1368 (Fed. Cir. 2000). "It is not unusual that separate claims may define the invention using different terminology, especially where (as here) independent claims are involved." *Hormone Research Found. v. Genentech, Inc.*, 904 F.2d 1558, 1567 n.15 (Fed. Cir. 1990). *See also Nystrom*, 424 F.3d at 1143. (CL 7.)

The term "parent *Bacillus stearothermophilus* alpha-amylase" in claims 1 and 5 should be construed to mean "an alpha-amylase having the amino acid sequence of SEQ ID NO:3." (CL 12.)

(3) Genencor's Alternate Construction – "*Bacillus stearothermophilus* Alpha-amylase" Means "a 514 or 515 Amino Acid Protein Encoded by the Wild Type *Bacillus stearothermophilus* Gene"

If the Court does not construe the term "*Bacillus stearothermophilus* alpha-amylase" to mean "SEQ ID NO:3," then that term should mean "a 514 or 515 amino acid alpha-amylase

encoded by a wild type *Bacillus stearothermophilus* gene, minus the signal sequence.” (FF 143; CL 13.) This alternate definition is consistent with the teachings of the ’031 Patent and with all evidence available to a protein engineer in 1995, as Novozymes’ expert Dr. Arnold agrees.

(a) *Every Bacillus stearothermophilus alpha-amylase disclosed in the ’031 Patent has 514 or 515 amino acids*

All three examples of *Bacillus stearothermophilus* alpha-amylases in the ’031 Patent have 514 or 515 amino acids. Gray *et al.* shows a wild type *Bacillus stearothermophilus* alpha-amylase having 515 amino acids. (Alber, Tr. at 222:18-223:9, A-5223-5224; TE 100 at 11, col. 7:32-35, A-7011.) (FF 144.) Figure 1 of the ’031 Patent presents the amino acid sequence of a *Bacillus stearothermophilus* alpha-amylase having 514 amino acids. (Alber, Tr. at 223:22-224:9, A-5224-5225; TE 100 at 11, col. 7:32-35, A-7011.) (FF 145.) The “sequence listing” presents an amino acid sequence, designated “SEQ ID NO:3,” of a third *Bacillus stearothermophilus* alpha-amylase, which also has 514 amino acids. (Alber, Tr. 224:11-24, A-5225; TE 100 at 30-32, cols. 45-50, A-7030-7032.) (FF 146.) The ’031 Patent does not teach any *Bacillus stearothermophilus* alpha-amylase of any other length.

(b) *All Bacillus stearothermophilus alpha-amylases reported in the literature as of 1995 had 514 or 515 amino acids*

The exemplary and definitional disclosures of the ’031 Patent are consistent with all of the contemporaneous literature available to a protein engineer in 1995, as well. As described at trial, papers published by at least eight research groups from 1985 to 1995 reported genes from wild type *Bacillus stearothermophilus* strains that encoded preproteins of 548 or 549 amino acids that are processed to alpha-amylases of 514 or 515 amino acids by removal of their N-terminus signal sequences. (Alber, Tr. at 209:2-18, A-5210, 209:25-210:5, A-5210-5211, 211:6-212:3, A-5212-5213, 212:19-214:8, A-5213-5215; TE 568 at 2, Abstract, A-8944; TE 628 at 1, Abstract and 2, A-8993-8994; TE 629 at 3, ¶ bridging columns, A-9005; TE 630 at 6, Fig. 2 and its legend, A-9018; TE 633 at 1, Summary, A-9025; TE 634 at 4, col. 1, A-9034; TE 635 at 1,

Abstract, A-9037.) All publications as of 1995, and later, report that alpha-amylases have 514 or 515 amino acids. (Alber, Tr. at 215:9-12, A-5216.) (FF 148-161.)

Novozymes' expert, Dr. Arnold, agreed at trial that in 1995 a skilled protein engineer would have expected an alpha-amylase expressed from an alpha-amylase gene of a wild type *Bacillus stearothermophilus* to have 514 or 515 amino acids. (Arnold, Tr. at 180:1-6, A-5181.) Dr. Arnold also admitted that as of March 1995, there was no evidence in the published literature of any alpha-amylase expressed from a wild type *Bacillus stearothermophilus* gene that was truncated at its C-terminus. (Arnold, Tr. at 180:7-12, A-5181).⁴ (FF 167.)

(c) *Genencor's G-ZYME® G997 product is not a "Bacillus stearothermophilus alpha-amylase"*

Novozymes is expected to contend that Genencor's G-ZYME® G997 product, a fermentation product of the *Bacillus stearothermophilus* strain G997, is the "parent *Bacillus stearothermophilus* alpha-amylase" to which SPEZYME® Ethyl should be compared to evaluate infringement. The G-ZYME® G997 product is not a "parent *Bacillus stearothermophilus* alpha-amylase" within the meaning of the '031 Patent, because it is the product of an industrial process, and not a 514 to 515 amino acid wild type alpha-amylase. (Alber, Tr. at 249:23-250:4, A-5250-5251, 260:25-261:12, A-5261-5262.) (FF 168, 174.)

The effects of industrial processing disqualify the product G-ZYME® G997 as a "parent." (See FF 175-176, discussing conditions of industrial processing and effects on proteins.) The trial record shows that there is no single, unvarying protein sequence of the G-ZYME® G997 product. Dr. Jorgensen admitted at trial that he could not say that all samples of G-ZYME® G997 would

⁴ Dr. Jorgensen's recent sequencing of Genencor's G-ZYME® G997 commercial product, revealing a truncation at its C-terminus, was not available in 1995, so it plainly would not have been taken into account by a protein engineer in 1995 in arriving at a definition of "Bacillus stearothermophilus alpha-amylase." (Alber, Tr. at 225:13-226:5, A-5226-5227; Jorgenson, Tr. at 663:20-23, A-6071.) Even if Dr. Jorgensen's data were available, a protein engineer in 1995 would not have considered it to be proof of the structure of a wild type, naturally occurring *Bacillus stearothermophilus* alpha-amylase (Alber, Tr. at 228:6-11, A-5229), because the truncation observed was in an industrial product and was contrary to all reports in the literature noted above. (*Id.*) (FF 165-166.)

have the same sequence as that he determined, nor could he say that the sequence of G-ZYME® G997 is always the same. (Jorgensen, Tr. at 80:18-21, A-5080, 83:10-13, A-5083, 83:23-25, A-5083.) (FF 170.) Genencor's analysis of G-ZYME® G997 before this litigation confirms that the G-ZYME® G997 product included multiple alpha-amylases of different lengths—there were three different deletions at the C-terminus, indicating a mixture of three proteins, with 27, 28, or 29 amino acids deleted. (Alber, Tr. at 249:13-17, A-5250, 280:6-19, A-5511, 286:11-14, A-5517, 291:12-292:9, A-5522-5523, 302:10-14, A-5533; TE 161, A-8365-8374.) (FF 171.)

The alpha-amylase gene of *Bacillus stearothermophilus* strain G997 encodes an alpha-amylase of 515 amino acids after removal of the signal sequence. (TE 161 at 4, A-8368.) Sequencing by both Novozymes and Genencor shows that Genencor's G-ZYME® G997 product is missing at least 27, 28, or 29 amino acids (present in the wild type) from the C-terminus. That same sequencing shows that the amino acid sequence is variable and uncertain. G-ZYME® G997 is not, therefore, a "*Bacillus stearothermophilus* alpha-amylase" as understood by a protein engineer as of 1995. (Alber, Tr. at 249:23-250:4, A-5250-5251, 260:25-261:12, A-5261-5262.) (FF 172-173.)

(4) “% Homology”: A Protein Engineer in 1995, Instructed by the '031 Patent, Would Have Counted All Deletions in Computing % Homology Between Alpha-amylases

(a) *The '031 Patent does not require use of the GAP (GCG) program*

Ignoring the '031 Patent's statement that in calculating “% homology” (or “% identity” (Arnold, Tr. at 140:6-14, A-5141; Alber, Tr. at 294:5-9, A-5525)) between two amino acid sequences the GAP (GCG) program “*may* suitably be used” (TE 100 at 9, col. 4:36-45, A-7009 (emphasis added)), Novozymes construes the term “at least 95% homology” as “sequence identity determined *solely* by the GAP (GCG) computer program.” This is wrong. The '031 Patent does not require the use of GAP (GCG). (FF 186, 193, 201, 213.)

The '031 Patent defines "X % homologous to another amino acid sequence" as:

An amino acid sequence is considered to be X % homologous to the parent α -amylase, if a comparison of the respective amino acid sequences, performed via known algorithms, such as the one described by Lipman and Pearson in *Science* 227 (1985) p. 1435, reveals an identity of X %. The GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used, employing default values for GAP penalties [Genetic Computer Group (1991) Programme Manual for the GCG Package, version 7, *i.e.*, 575 Science Drive, Madison, Wis., USA 53711].

(TE 100 at 9, 4:36-45, A-7009.) This passage does not give complete instructions about how to calculate % homology. (Alber, Tr. at 233:1-16, A-5234.) It states that sequence alignment can be performed "via known algorithms" – exemplified by the Lipman and Pearson reference and the GAP (GCG) program – and that the percent homology is "revealed" from the alignment, but how the percent identity is "revealed" is unclear.⁵ (FF 186, 191.)

The Lipman and Pearson algorithm called out in the '031 Patent does not disclose how to calculate % homology (Alber, Tr. at 234:1-20, A-5235). And, the GAP (GCG) program is only suggested by the '031 Patent, not required. (Devereux, Tr. at 128:19-129:6, A-5129-5130.) As Novozymes' expert Dr. Arnold agreed, another program may be used or the calculation may be performed by hand. (Alber, Tr. at 234:25-235:8, A-5235-5236; Arnold, Tr. 181:12-182:10, A-5182-5183.) Dr. Arnold also admitted that there was no pattern or practice amongst those of ordinary skill in the art regarding determination of percent homology (Arnold, Tr. at 190:19-191:3, A-5191-5192), and that approaches for sequence alignment and/or calculation of percent identity available as of March 29, 1995 might have given a different % homology than the GAP (GCG) program for the same pair of sequences. (Arnold, Tr. at 181:22-24, A-5182.) (FF 192-194.)

⁵ Determining "percent homology" or "percent identity" of two sequences is a two-step process. First, one "aligns" the two sequences by matching up identical residues in the sequences and, second, one calculates % identity using the alignment. (Devereux, Tr. at 126:9-12, A-5127; Arnold, Tr. at 145:14-20, A-5146; Alber, Tr. at 233:22-24, A-5234.) (FF 188.)

(b) *The '031 Patent teaches the protein engineer to count all sequence differences, including deletions*

The protein engineer is not left without guidance in selecting a way to calculate % homology. The teachings of the '031 Patent and scientific literature direct a protein engineer to use a method that accounts for all deletions, including those at the C-terminus. (See FF 201-212.)

Specifically, there are a number of statements in the '031 Patent that instruct the protein engineer to consider all types of sequence changes, including substitutions, insertions, and deletions (Alber, Tr. at 238:1-5, A-5239), which Dr. Borchert agreed were the types of changes relevant to protein engineering. (Borchert, Tr. at 23:9-23, A-5023.) For example, at col. 3, lines 59-65, the '031 Patent states that the variants of the invention include those in which “at least one amino acid residue of the parent α -amylase has been deleted,” which teaches a protein engineer that even one amino acid that has been deleted should be counted in a % homology calculation. (Alber, Tr. at 238:20-239:7, A-5239-5240.) The '031 Patent also provides a nomenclature to describe all sequence differences, including deletions. (Alber, Tr. at 239:8-11, A-5240; TE 100 at 10, 6:36-62, A-7010.) Since the '031 Patent provides a nomenclature for specifying deletions, a protein engineer in 1995 reading the patent would have understood that it is necessary and important to count all deletions when calculating % homology. (Alber, Tr. at 239:12-16, A-5240, 295:6-297:24, A-5526-5528.) (That deletions are the core of the alleged invention also strongly suggests that they should be counted. (Alber, Tr. at 237:22-25, A-5238.)) (FF 201-206.)

Novozymes agreed that the teachings of the '031 Patent require counting all deletions – at least, it did until it sued Genencor. Dr. Arnold previously submitted a declaration to this Court concerning a related patent with the same specification (claiming different variants of SEQ ID NO:3) in litigation among Novozymes, EDC, and Enzyme Bio-Systems Ltd. (later purchased by Genencor). (TE 511, A-8875-8900.) In that declaration, Dr. Arnold provided an explicit definition of “percent homology” in the context of the same specification as the '031 Patent specification, stating that in determining % homology one should take into account additions,

substitutions, and deletions. (TE 511 at 12, ¶ 30, A-8886; Arnold, Tr. at 185:7-21, A-5186.) (FF 207.) The same approach is mandated here.

Finally, in addition to the '031 Patent's teachings to count all deletions, and Dr. Arnold's admission, there are scientific reasons why a protein engineer would select a method of calculating % homology that accounts for deletions, specifically those at the C-terminus. The 1995 Vihinen paper shows that the C-terminus of *Bacillus stearothermophilus* alpha-amylase is important for the enzymatic activity, *i.e.*, function and stability of the alpha-amylase. (Alber, Tr. at 216:9-217:6, A-5217-5218, 217:20-218:20, A-5218-5219.) (FF 210.) Knowing this dependence of enzyme activity and stability of the alpha-amylase on its C-terminus region would have led a skilled protein engineer in 1995 to count deletions in this region when computing % homology between alpha-amylases. (Alber, Tr. at 218:21-219:2, A-5219-5220; Arnold, Tr. at 176:19-177:13, A-5177-5178.) (FF 212.) Thus, in comparing SPEZYME® Ethyl to an alleged "parent" in context of the claims of the '031 Patent, a protein engineer in 1995 would have considered a truncation of amino acids at its C-terminus to be a sequence change in SPEZYME® Ethyl that should be counted in calculating % homology. (Alber, Tr. at 205:15-24, A-5206.) (FF 19, 209.)

(c) *% homology obtained using the GAP (GCG) program*

In contrast to the teachings of the '031 Patent, the GAP (GCG) program does not count "gaps," *i.e.*, regions where there is no residue in one sequence corresponding to a residue in the other sequence, in calculating % identity. (Devereux, Tr. at 111:9-12, A-5112.) Instead, the GAP (GCG) program calculates % identity between two aligned sequences by taking the sum of all of the exactly matching residues and dividing that number by the number of residues aligned. (Devereux, Tr. at 110:2-6, A-5111.) This means that GAP (GCG) does not count deletions within or at the end of a sequence. (FF 197.)

Thus, because GAP (GCG) does not count deletions, two amino acid sequences that are less than 100% identical due to deletions would still have a 100% identity according to the GAP

(GCG) program. (Devereux, Tr. at 116:10-117:7, A-5117-5118.) GAP (GCG) also ignores the functional effect of deletions while telling a protein engineer that two different sequences are 100% “identical.” (Devereux, Tr. at 121:10-25, A-5122, 122:1-4, A-5123, 122:23-123:6, A-5123-5124.)⁶ Using this approach to calculate % identity produces nonsensical results for a protein engineer trying to apply the teachings of the ’031 Patent. (Alber, Tr. at 235:9-21, A-5236.) (FF 196, 199.)

- (d) *A protein engineer in 1995 would have known how to apply the teachings of the ’031 Patent to calculate % identity and still count deletions*

The ’031 Patent’s suggestion that one may suitably use the GAP (GCG) program, which ignores deletions, appears inconsistent with the teachings of the ’031 Patent, which instruct one to count deletions in comparing a variant to its parent. (Alber, Tr. at 239:22-240:5, A-5240-5241.) A protein engineer in 1995, in following the teachings of the ’031 Patent, would have had several methods to resolve the apparent inconsistency, however, all of which are consistent with the teachings of the ’031 Patent. (Alber, Tr. at 240:6-10, A-5241, 241:5-16, A-5242.) (FF 213-214.)

- (i) Modified GAP (GCG)

The first method that resolves the apparent inconsistency in the ’031 Patent is to use the GAP (GCG) program to align the two sequences to be compared, and to then calculate % identity by hand. A protein engineer would take the number of residues that are identical in an alignment and divide it by the total number of residues in the larger sequence, including gap positions. (Alber, Tr. at 241:17-242:5, A-5242-5243.) Dr. Devereux agreed that the GAP (GCG) program could be used in this manner. (Devereux, Tr. at 127:4-9, A-5128.) Applying this approach to calculating the % homology between SPEZYME® Ethyl and SEQ ID NO:3 accounts for the

⁶ One would obtain an identity of one hundred percent with the GAP (GCG) program if one aligns two amino acid sequences that are vastly different in length but identical in the overlapping portion. (Devereux, Tr. at 110:7-17, A-5111, 111:9-12, A-5112.) This would be so even if one of the sequences extended over the other by a “tail” of a thousand amino acids, and even if the “tail” made a functional difference to the protein. (Devereux, Tr. at 121:10-25, A-5122, 122:1-4, A-5123, 122:23-123:6, A-5123-5124.) (FF 199.)

entire deletion of 30 residues at the C-terminus of SPEZYME® Ethyl (as compared to its parent) and, thus, compares all of SPEZYME® Ethyl to all of SEQ ID NO:3. (Alber, Tr. at 242:6-11, A-5243.) (FF 200, 216.)

(ii) Other programs that count deletions

Alternatively, a computer program that accounts for deletions could be used. At least two such programs existed as of March 29, 1995, the “Align” and “GAP (Huang)” programs. After aligning sequences, the Align and GAP (Huang) compute % identity in a manner that counts all substitutions, additions, and deletions, thereby counting all sequence differences, including the amino acids of an extension of one sequence beyond the end of the other sequence and the amino acids of any internal gaps. (Pearson, Tr. at 310:22-311:12, A-5541-5542, 312:20-22, A-5543, 314:5-315:15, A-5545-5546, 317:8-23, A-5548; Huang, Tr. at 333:15-334:23, A-5564-5565, 334:5-18, A-5565, 336:25-337:4, A-5567-5568, 338:3-10, A-5569; Alber, Tr. at 242:12-243:4, A-5243-5244.) (FF 217-219.)

(iii) By hand

An alternative method is to do the alignment “by eye” and the calculation of % homology “by hand.” (Alber, Tr. at 243:5-12, A-5244.) One would count the number of identical corresponding residues in the alignment and divide that by the total number of residues in the aligned sequences. (Alber, Tr. at 243:9-12, A-5244.) Such “by hand” alignment between SPEZYME® Ethyl and SEQ ID NO:3 could have been done by a protein engineer in 1995. (Alber, Tr. at 243:13-20, A-5244.) (FF 220.)

C. SPEZYME® Ethyl Does Not Literally Infringe Claim 1

Evaluating infringement of claims 1, 3, and 5 requires a comparison of SPEZYME® Ethyl and its alleged “parent,” and then some simple arithmetic. Comparing the proper parent, and accounting for all deletions, as taught by the ’031 Patent, leads to a simple answer – SPEZYME® Ethyl does not literally infringe any asserted claim of the ’031 Patent.

(1) Genencor's Construction of "*Bacillus stearothermophilus* Alpha-amylase"

If the phrase "*Bacillus stearothermophilus* alpha-amylase" in claim 1 means "SEQ ID NO:3," then claim 1 is not infringed by SPEZYME® Ethyl because its amino acid sequence does not have "at least 95% homology" to SEQ ID NO:3 using any appropriate method that accounts for all substitutions, insertions, and deletions over the entire sequence alignment. Calculating % homology between the amino acid sequences of SPEZYME® Ethyl and SEQ ID NO:3 using "GAP GCG modified," the Align program, the GAP (Huang) program, or "by hand," one always obtains a % homology of less than 95%. (Alber, Tr. at 245:2-7, A-5246.) Because SPEZYME® Ethyl does not satisfy the limitation of claim 1 that it have "at least 95% homology" to SEQ ID NO:3 (Genencor's Construction), claim 1 is not infringed. (CL 21-22.)

(2) Genencor's Alternate Construction of "*Bacillus stearothermophilus* Alpha-amylase"

The only difference between Genencor's Construction and its Alternate Construction is the definition of the term "*Bacillus stearothermophilus* alpha-amylase." Under Genencor's Alternate Construction, the term "*Bacillus stearothermophilus* alpha-amylase" means a 514 or 515 amino acid protein encoded by a wild type *Bacillus stearothermophilus* alpha-amylase gene (minus the signal sequence). For purposes of this analysis, therefore, the "worst case" will be assumed in which (a) the alpha-amylase has 514 amino acids (a 515 amino acid protein where the additional position is a deletion would lower the % homology) and (b) the amino acid sequence is identical to that of SPEZYME® Ethyl, except for the positions of the 179-180 "RG" deletion and the C-terminus truncation (such identity would give the highest % homology). (CL 23-24.)

Calculating % homology between the amino acid sequences of SPEZYME® Ethyl and the 514 amino acid protein of the "worst case" under Genencor's Alternate Construction by "GAP (GCG) modified," by the Align program, by the GAP (Huang) program, or "by hand," one always obtains a % homology that is less than 95%. (Alber, Tr. at 245:8-18, A-5246.) Because SPEZYME® Ethyl does not satisfy the limitation of claim 1 that it have "at least 95% homology"

to the “worst case” under Genencor’s Alternate Construction, claim 1 is not infringed. (CL 25-26.)

D. SPEZYME® Ethyl Does Not Literally Infringe Claim 3

Using any appropriate method that accounts for all substitutions, insertions, and deletions, including internal and terminal deletions, over the entire sequence alignment, SPEZYME® Ethyl does not have “at least 95% homology” to SEQ ID NO:3. (Alber, Tr. at 247:19-24, A-5248.) Because SPEZYME® Ethyl does not satisfy the limitation of claim 3 that it have “at least 95% homology” to SEQ ID NO:3, claim 3 is not infringed. (CL 29-30.)

E. SPEZYME® Ethyl Does Not Literally Infringe Claim 5

SPEZYME® Ethyl is a variant of the 515-amino acid alpha-amylase encoded by the alpha-amylase gene of strain G997, its parent. (FF 54-56; CL 31.) Claim 5 recites that “the alpha-amylase variant consists of a deletion of amino acids 179 and 180, using SEQ ID NO:3 for numbering.” (TE 100 at 40, col. 66:18-20, A-7040 (emphasis added.)) This means that the deletion of amino acids 179 and 180 is the only permissible difference between the alleged infringing product and its parent. *See Norian Corp. v. Stryker*, 363 F.3d 1321, 1331-32 (Fed. Cir. 2004). (Arnold, Tr. at 146:12-23, A-5147; Alber, Tr. at 248:3-9, A-5249.) (CL 31-32.)

(1) Genencor’s Construction of “Bacillus stearothermophilus Alpha-amylase”

If the term “*Bacillus stearothermophilus* alpha-amylase” in claim 5 means “SEQ ID NO:3,” then claim 5 is not infringed because, when one compares the amino acid sequence of SPEZYME® Ethyl to that of SEQ ID NO:3, SPEZYME® Ethyl has changes from SEQ ID NO:3 in addition to the deletion of amino acids 179 and 180. (Alber, Tr. at 248:10-19, A-5249.) Those other changes are five different amino acid substitutions throughout the body of the protein and the deletion of 30 amino acids from the C-terminus of SEQ ID NO:3. (Alber, Tr. at 248:19-21, A-5249.) Because SPEZYME® Ethyl does not satisfy the limitation of claim 5 that it “consist of”

a deletion of amino acids 179 and 180 when compared to the amino acid sequence of SEQ ID NO:3, claim 5 is not infringed. (CL 33-34.)

(2) Genencor's Alternate Construction of "*Bacillus stearothermophilus* Alpha-amylase"

If the phrase "*Bacillus stearothermophilus* alpha-amylase" in claim 5 means the protein of the "worst case" under Genencor's Alternate Construction, then claim 5 is not infringed because, when one compares the amino acid sequence of SPEZYME® Ethyl to any 514 or 515 amino acid wild type *Bacillus stearothermophilus* alpha-amylase, SPEZYME® Ethyl contains at least the deletion of 30 or 31 amino acids at the C-terminus in addition to the deletion of amino acids 179 and 180. (Alber Tr. at 248:22-249:2, A-5249-5250.) Because SPEZYME® Ethyl does not satisfy the limitation of claim 5 that it "consist of" a deletion of amino acids 179 and 180 when compared to a 514 or 515 amino acid wild type *Bacillus stearothermophilus* alpha-amylase, claim 5 is not infringed. (CL 37-38.)

F. **Novozymes Cannot Show Infringement if G-ZYME® G997 is the "Parent *Bacillus stearothermophilus* Alpha-amylase"**

Novozymes cannot meet its burden of proof to show literal infringement by SPEZYME® Ethyl even if it prevails on its definition of "parent." Novozymes apparently contends that the protein of the G-ZYME® G997 product is the "parent *Bacillus stearothermophilus* alpha-amylase" to be compared to SPEZYME® Ethyl. The problem is that Novozymes has presented the Court with at least four different amino acid sequences produced from DNA encoding the same alpha-amylase from the wild type genes of *Bacillus stearothermophilus* strains G997 and ATCC 31,195. Novozymes presented different sequences for G-ZYME® G997 from Judy Chang's pre-litigation analysis, another from Dr. Jorgenson, and still more sequences from analysis of ATCC 31,195, which encodes the same protein as strain G997 (after removal of the

signed sequence). This uncertainty is fatal to G-ZYME® G997 as a “parent.”⁷ (FF 169, 171, 178-183; CL 40.)

Claims 1, 3, and 5 require a comparison of the amino acid sequence of the alleged “parent” with the amino acid sequence of the accused product. Because the amino acid sequence of G-ZYME® G997 is uncertain and variable, it is impossible to make a mathematically or otherwise certain comparison of the amino acid sequence of G-ZYME® G997 to any accused product, including SPEZYME® Ethyl. Thus, Novozymes cannot meet its burden to show literal infringement by SPEZYME® Ethyl if G-ZYME® G997 is the “parent.” (CL 40.)

IV. CLAIMS 1, 3, AND 5 OF THE '031 PATENT ARE INVALID

A. Claims 1, 3, and 5 Are Invalid as Obvious

(1) Summary of the Legal Standard

In determining whether a claim is invalid as obvious under 35 U.S.C. § 103(a), the Court should consider: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372-73 (Fed. Cir.) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)), *cert. denied*, 126 S. Ct. 488 (2005). Upon establishment of a *prima facie* case of obviousness, the burden shifts to the patentee to come forward with evidence to rebut that case, for example, by evidence of unexpected results. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Such results must be shown to be unexpected compared with the closest prior art. *See id.*; *In re Mayne*, 104 F.3d 1339, 1341-42 (Fed. Cir. 1997); MPEP §§ 716.02(b), 716.02(e). Where the differences revealed in comparative testing are a matter of “degree” rather than a difference “in kind,” the

⁷ Given the uncertainty and variability of the protein in the G-ZYME® G997 product, if that product is the “parent” against which SPEZYME® Ethyl is to be compared for evaluating infringement, the asserted claims are similarly uncertain and variable. If one cannot tell whether a product infringes because the claim is indefinite, the claim does not fulfill its notice function and is invalid under 35 U.S.C. § 112, ¶ 2. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003).

alleged unexpected results will not overcome the *prima facie* finding of obviousness. *In re Merck Co., Inc.*, 800 F.3d 1091, 1099 (Fed. Cir. 1986). (CL 42-46.)

(2) The Combination of Suzuki and the Bisgard-Frantzen PCT Renders Obvious the Asserted Claims.

Novozymes has never disputed that the claimed *Bacillus stearothermophilus* alpha-amylase (“BSG”) with a deletion of amino acids 179 and 180 is *prima facie* obvious over Suzuki in view of the Bisgard-Frantzen PCT. (FF 29, 38; CL 47.) In fact, Novozymes’ expert Dr. Arnold admitted that Suzuki would have provided the motivation for one to make the deletion of residues 179 and 180 in BSG to increase thermostability of BSG. (Arnold, Tr. at 742:9-11, A-6530). (FF 107; CL 48.)

Novozymes’ sole response to Suzuki and the Bisgard-Frantzen PCT is the alleged “unexpected results” of the Borchert Declaration. That Declaration completely fails to carry Novozymes’ burden to overcome the admitted obviousness of the ’031 Patent, because:

- *The Borchert experiment was not a fair comparison to Suzuki.* Although Mr. Garbell testified that he chose to test thermostability because that was the focus of Suzuki, there were numerous differences between Dr. Borchert’s “experiment” and Suzuki’s work. Unlike Suzuki, Dr. Borchert failed to pre-heat the buffer or otherwise account for “ramp-up” in BAN WT; he also conducted his “experiment” at a lower temperature and much lower calcium concentration. (Cf., TE 115 at 18934, A-8234, TE 508 at ¶ 5, A-8858.) The effect of these changes was to enhance the relative improvement of BSG compared to BAN. (Borchert, Tr. at 26:17-22, A-5026; Klibanov, Tr. at 527:18-528:3, A-5758-5759.) (FF 104-106; CL 54-55, 99.)
- *The Borchert Declaration does not show unexpected results.* The Borchert Declaration shows a relative improvement in BSG of the same order of magnitude as the improvement in BAN shown in Suzuki, which would not have been unexpected to a

protein engineer. This difference in degree, not in kind, cannot overcome the admitted *prima facie* obviousness of the '031 Patent. (FF 132-134; CL 53, 101.)

- *The numerous deficiencies in the Borchert “experiment” make it so unreliable that the Borchert Declaration does not prove unexpected results.* Borchert’s failure to account for “ramp-up” in the heating of BAN WT doubled the calculated half-life of BAN WT, and as a result underestimated the improvement of BAN del. Improper omission of data points and impermissible extrapolating of the half-life for BSG del overstated the improvement in BSG. (Klibanov, Tr. at 533:13-535:2, A-5764-5766; Borchert, Tr. at 384:22-24, A-5615, 386:9-12, A-5617.) The comparison of relative improvement in the Borchert Declaration is therefore unreliable. (FF 107-131; CL 54-55, 100.)

The numerous problems with the Borchert Declaration can be explained by the fact that it was a critical step in Novozymes’ scheme to coax the Examiner into issuing broad claims, targeted at Genencor. Knowing it could not respond on the merits to the Examiner’s rejection based on Suzuki and the Bisgard-Frantzen PCT, Novozymes instead created a “straw man” — narrow claims it never intended to accept — to buy time to concoct “unexpected results” against art that Novozymes knew was not the closest prior art. Novozymes’ “experiment” was conducted under very different conditions from Suzuki (unpreheated buffer, low calcium concentration, and low temperature), which Novozymes did not discuss with the Examiner and which Dr. Borchert knew might affect the results. (CL 108.)

The Borchert Declaration does not present legally sufficient “unexpected results” to rebut the *prima facie* obviousness of the '031 Patent based on Suzuki and the Bisgard-Frantzen PCT. Without that rebuttal, Novozymes’ admission of obviousness is dispositive. (CL 56.) Claims 1, 3, and 5 of the '031 Patent are invalid as obvious under 35 U.S.C. § 103(a). (CL 57.)

(3) Machius '95 Alone Renders Obvious the Asserted Claims

Machius '95 is closer prior art⁸ than Suzuki and presents an even stronger case that claims 1, 3, and 5 of the '031 Patent are obvious. And, Machius '95 was not cited in the '031 Patent prosecution. Thus, no deference with respect to Machius '95 is due to the Examiner's decision to allow the '031 Patent claims at issue. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000). (FF 60-61, 95; CL 61.)

The invention of the '031 Patent is obvious if, considering the scope and content of the prior art, the level of ordinary skill in the art, the differences between the alleged invention of the '031 Patent and the prior art, and any objective indicia of nonobviousness, a protein engineer of ordinary skill would have been motivated to make the 179-180 deletion in BSG and would have had a reasonable expectation of success that in so doing the thermostability of BSG would be improved. *See In re Kahn*, 441 F.3d 977, 987 (Fed. Cir. 2006); *Graham*, 383 U.S. at 17-18; *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988). (CL 41-46.) Taking all of those factors together, the '031 Patent is demonstrably obvious in view of Machius '95.

The problem confronted by a protein engineer and allegedly solved by the invention of the '031 Patent is increasing thermostability of BSG. The '031 Patent purportedly solves that problem by making a deletion of the RG amino acids at positions 179-180 of BSG, using SEQ ID NO:3 for numbering. (CL 68.)

Machius '95 addresses the identical problem as the '031 Patent. (*See, e.g.*, TE 173 at 551-553, A-8382-8384.) As Novozymes has admitted, Machius '95 summarizes the teachings of Suzuki, which Novozymes has also admitted renders obvious the invention of the '031 Patent. (*Id.* at 553, A-8384.) (CL 62.) Suzuki examined the effect on thermostability in BAN

⁸ Machius '95 is prior art to the '031 Patent because it was published at least as early as March 13, 1995 (see cover page of TE 173 showing library date stamp, A-8375), before the earliest possible effective filing date of the '031 Patent. Novozymes has admitted that March 29, 1995 is the critical date. (Proposed Final Pretrial Order, D.I. 85 at 29-30, A-1029-1030.) (FF 20-23; CL 58-60.)

(comparing it to BLA) of a deletion corresponding to the 179-180 deletion in BSG of the '031 Patent. However, Machius '95 goes well beyond Suzuki by teaching, as Novozymes also admits, that positions 179-180 are in an exposed surface loop and that shortening that loop would likely increase thermostability. While the structure studied in Machius '95 was that of BLA, Machius '95 expressly teaches that the three-dimensional structures of BLA and BSG (which Machius '95 refers to as BStA) would be expected to be similar. (FF 68-74; CL 62, 68-69.)⁹

Novozymes and its expert have already admitted that a protein engineer of ordinary skill in 1995 would have been motivated to make the 179-180 deletion in BSG based on the teachings of Suzuki; indeed, Novozymes' expert argues as much in attempting to diminish the importance of Machius '95. In fact, Machius '95 goes further by resolving possible concerns regarding areas of "interaction," in the region of the deletion discussed in Suzuki. As Dr. Machius testified, without any rebuttal from Novozymes or Dr. Arnold, upon reading the teachings of Machius '95, an ordinarily skilled protein engineer would have had increased motivation to make the 179-180 deletion in BSG, and would also have had increased expectation of success (more than a "reasonable expectation" — it would have been a "no-brainer"). (Machius, Tr. at 484:1-485:6, A 5715-5716; 774:3-22, A 6562.) (FF 85.) Thus, Machius '95 alone renders obvious the invention of the '031 Patent. (CL 70.)

Novozymes' criticisms of Machius '95 do not detract from its teachings regarding the structural basis for the increased thermostability caused by deletion in Region I:

⁹ Note also that, prior to the publication of Machius '95, it was known that the amino acid sequences of BLA, BSG, and BAN were homologous and one of ordinary skill would have concluded that the three-dimensional structures were likely very similar. However, this conclusion was not stated by either Suzuki or the Bisgard-Frantzen PCT. Suzuki did not align the amino acid sequences of all three enzymes; for this alignment, Suzuki had to be combined with another reference, such as the Bisgard-Frantzen PCT. In contrast, Machius '95 contains the alignment of the three *Bacillus* amylase sequences and states that their three-dimensional structures were expected to be similar. Thus, Machius '95 makes explicit statements about the similarity of the three-dimensional structures not made by any other single reference of record in the prosecution of the '031 Patent, and, in addition, it need not be combined with any other reference for an alignment of all three *Bacillus* amylase sequences. For these additional reasons, it is closer prior art than Suzuki. (FF 69-74.)

- *Novozymes' attacks on the Machius '95 structure do not undermine the express teachings of Machius '95.* Suzuki Region I, wherein lies the 179-180 deletion, is in an exposed surface loop.¹⁰ There was not a shred of contrary testimony at trial (Novozymes' crystallography expert Dr. Davies was present but did not even testify in response to Dr. Machius). (FF 77-78; CL 71.)
- *The availability of atomic coordinates does not change the basic teachings of Machius '95.* It was not necessary for a protein engineer to have the atomic coordinates to understand that Suzuki Region I, despite Novozymes' criticisms, is still a surface loop.¹¹ (FF 80-82; CL 71.)
- *The Machius 1998 paper supports Machius'95.* While the 1998 paper shows some differences in the BLA structure from that illustrated in Machius '95, it fully supports the core teachings of Machius '95. Dr. Machius and colleagues determined a structure of BLA that contained calcium and was not cleaved. The 1998 structure confirmed that Suzuki Region I is in a surface loop. (Machius, Tr. at 473:10-476:9, A-5704-5707; TE 175, A-8391-8402.) (FF 79; CL 71.)

¹⁰ The issues with the structure were disclosed by the authors. The fact that the BLA crystallized by Dr. Machius and colleagues lacked the metal ions required for catalytic activity, was cut in the middle of the protein chain after residue 189 and residues 182-192 could not be resolved were all explicitly set out in the abstract of Machius '95 and in the body of the reference. (TE 173, A-8375-8390.) The authors, one of whom is a Nobel-prize winner for his work in X-ray crystallography, did not qualify their statement regarding the location of Region I in a surface loop, which loop was well resolved in the structure. (Machius, Tr. at 470:23-473:7, A-5701-5704.) (FF 60, 77-78.)

¹¹ This “issue” is really a red herring. Because there is significant information in papers reporting a crystal structure of a protein and the sheer length of the coordinates, scientists typically do not publish the coordinates with the paper. (Machius, Tr. at 777:10-17, A-6565; TE 118, A-8251-8328.) Even inventors Borchert, Svendsen, and Bisgard-Frantzen, in a paper authored with Novozymes' expert Dr. Davies, did not release the coordinates for a crystal structure (of a *Bacillus* alpha-amylase, no less) until a year after the paper was published. (Machius, Tr. at 777:18-781:18, A-6565-6569; TE 102, A-8147-8156 and TE 103, A-8157-8168.) Nevertheless, as stated in the acknowledgements section of Machius '95, the coordinates were available from the authors upon request--if protein engineers in 1995 had wanted the coordinates, they could have gotten them. (Machius, Tr. at 477:15-478:17, A-5708-5709; TE 173 at 557, A-8388.) (FF 80-82.)

Machius '95 makes such a strong *prima facie* case of obviousness that even true “unexpected results” would not be sufficient to overcome its teachings. *See Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d at 1476, 1484 (Fed. Cir. 1997). Machius '95 is so strong, in fact, that Novozymes did not present any meaningful testimony in response. And, the Borchert Declaration is not sufficient to rebut the strong case of obviousness presented by Machius '95, even if the alleged results are taken at face value. (CL 65-67.)

Claims 1, 3, and 5 of the '031 Patent are invalid as obvious in view of Machius '95. (CL 72.)

B. **Claims 1 and 3 Are Invalid As Not Enabled**

(1) **Legal Standard**

The enablement requirement of 35 U.S.C. § 112, ¶ 11, has long demanded that the scope of the claims bear a reasonable relationship to the scope of enablement provided by the specification. *See In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). This requires that the “disclosure must adequately guide the [skilled] worker to determine, without undue experimentation,” possible examples of claimed compounds that will possess the alleged utility of the insertion (in this case, alpha-amylase activity). *See In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). (CL 73-74.)

Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991), is instructive as to what disclosure is required to enable a generic claim. In *Amgen*, the plaintiff had claims that encompassed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make erythropoietin (EPO) and a few biologically active analogs from such genes. *See Amgen*, 927 F.2d at 1214. “The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids.” *Id.* at 1213. The court succinctly summarized the facts and its conclusion:

Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity.

Id. at 1214. The '031 Patent fails to meet this standard. (CL 75.)

(2) Claims 1 and 3 Are Not Enabled

There are approximately 10^{70} possible variants that are 95% homologous to SEQ ID NO:3 and contain the required double deletion of amino acid residues 179 and 180, a number greater than the number of atoms in the Milky Way. (Alber, Tr. at 251:12-17, A-5252.) Of the 10^{70} possible variants, there are only a maximum of 1 in 10,000 amino acid sequences that would also have alpha-amylase activity, and thus be within the scope of claims 1 and 3. (Alber, Tr. at 252:17-20, A-5253.) (FF 231, 235; CL 76.)

As Dr. Arnold stated at trial, “[p]roteins are both complex and finely tuned by evolution and they are quite complex machines such that changing even a single amino acid can often have a deleterious effect.” (Arnold, Tr. at 136:4-7, A-5137.) The specification of the '031 Patent provides no general guidance as to which mutations in SEQ ID NO:3, other than a handful of mutations, will lead to proteins that are 95% homologous to SEQ ID NO:3, contain the required double deletion, and have alpha-amylase activity. Thus, considering the complexity of proteins and the astronomically large number of possible variants, that may or may not possess alpha-amylase activity, the specification of the '031 Patent does not provide sufficient disclosure to

enable an ordinarily skilled protein engineer to make the variants claimed in claims 1 and 3 without undue experimentation.¹² (FF 233, 236-237; CL 77.)

Claims 1 and 3 are not enabled and are invalid under 35 U.S.C. § 112, ¶ 1. (CL 78.)

V. THE '031 PATENT IS UNENFORCEABLE BECAUSE NOVOZYMES WAS GUILTY OF INEQUITABLE CONDUCT IN THE PROSECUTION OF THE '031 PATENT

A. Legal Standard for Inequitable Conduct

Patent applicants and their attorneys have a duty to prosecute applications in the PTO with candor, good faith, and honesty. *See Precision Instrument Mfg. Co. v. Automotive Maint. Mach. Co.*, 324 U.S. 806, 818 (1945); *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 n.8 (Fed. Cir. 1987); *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995); *eSpeed, Inc. v. Brokertec USA, L.L.C.*, No. Civ.A. 03-612-KAJ, 2006 WL 416860, at *7 (D. Del. Feb. 22, 2006). Breach of that duty by “affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive” renders a patent unenforceable due to inequitable conduct. *Molins PLC*, 48 F.3d at 1178. A party alleging inequitable conduct must prove it by clear and convincing evidence. *See id.* (CL 79-81.)

Materiality can be demonstrated in a variety of ways, ranging from “but for” causality (the misrepresentation literally caused the Examiner to issue the patent), to the test of former Rule 56 (would a reasonable patent Examiner have considered the information misrepresented or withheld important to her decision-making process), to the new Rule 56 (information is material

¹² To produce a single alpha-amylase that is 95% homologous to SEQ ID NO:3, a protein engineer would have to introduce appropriate nucleotide changes into DNA encoding SEQ ID NO:3, express the protein encoded by the DNA, purify the protein, and test the protein for alpha-amylase activity. (Alber, Tr. at 252:5-8, A-5253.) It would take a protein engineer longer than the age of the universe to produce a fraction of the 10⁷⁰ amino acid sequences that have 95% homology to SEQ ID NO:3 and contain the required double deletion, much less test them for alpha-amylase activity. (Alber, Tr. at 252:5-8, A-5253.) Since most random sequence changes to SEQ ID NO:3 would reduce its alpha-amylase activity or stability, only a small fraction of such changes would produce a protein with alpha-amylase activity and stability. (Alber, Tr. at 252:13-17, A-5253.) (FF 232, 234.)

if it establishes a *prima facie* case of invalidity or is inconsistent with arguments made to the Examiner). *See Digital Control Inc. v. The Charles Machine Works*, 437 F.3d 1309, 1318-19 (Fed. Cir. 2006); 37 C.F.R. § 1.56. (CL 84.)

Withheld prior art, then, is material if a reasonable Examiner would have considered the art important in deciding whether to grant a patent. *See Digital Control*, 437 F.3d at 1318-19. The MPEP expressly instructs prosecuting attorneys that, “when in doubt,” it is the appropriate course to submit information to the PTO to avoid questions concerning the disclosure of material information. MPEP §§ 2004, 2001.04, 2001.05. (CL 84.)

The required deceptive intent “need not be proven by direct evidence; it is most often proven by a showing of acts, the natural consequences of which are presumably intended by the actor.” *Molins PLC*, 48 F.3d at 1180. A persistent pattern of material misrepresentations on the part of the patentee can be tantamount to clear and convincing evidence of deceptive intent. *See PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1320 (Fed. Cir. 2000). (CL 85-86.)

Once threshold levels of materiality and intent have been shown, a court must engage in “a careful balancing: when the misrepresentation or withheld information is highly material, a lesser quantum of proof is needed to establish the requisite intent, In contrast, the less material the information, the greater the proof must be.” *Purdue Pharma L.P. v. Endo Pharm.*, 438 F.3d 1123, 1128-29 (Fed. Cir. 2006) (internal citations omitted). (CL 83.)

B. Inequitable Conduct Based on Non-Disclosure of Machius '95

Machius '95 explains why the Suzuki deletion, if made in BSG, would have been reasonably expected to substantially increase its thermostability (in fact, it was a “no-brainer”). (Machius, Tr. at 774:3-22, A-6562.) Machius '95 would have provided a basis for rejecting the claims that issued in the '031 Patent that was stronger than the art previously relied on by the Examiner. Faced with that high level of materiality, and under the commercial gun, Novozymes

never took the opportunity to “cure” its non-disclosure, even though the opportunity continually presented itself. (FF 68-74, 84-85.)

(a) *Dr. Borchert and Mr. Garbell’s familiarity with Machius ’95*

Dr. Borchert and Mr. Garbell were both very aware of the Machius ’95 reference during the ’031 Patent prosecution.¹³ Dr. Borchert had read the Machius ’95 paper closely after it was published (Borchert, Tr. at 360:22-361:8, A-5591-5592); he invited Dr. Machius to give a seminar at Novozymes (Borchert, Tr. at 361:9-15, A-5592; Machius, Tr. at 468:20-469:1, A-5699-5700); he incorporated a discussion of Machius ’95 into seminars he gave (Borchert, Tr. at 361:16-362:19, A-5592-5593; TE 664 at GCOR170281, A-9048) and papers he wrote (TE 102 at 1, 4-5, A-8147, 8150-8151); he cited Machius ’95 in support of a different patent; and he discussed Machius ’95 in a deposition and declaration in the interference proceeding pending during prosecution of the ’031 Patent. (Borchert, Tr. at 368:11-372:3, A-5599-5603; TE 524 at 13, ¶¶ 38 and 39, A-8915, and 14, ¶ 43, A-8916.)

Mr. Garbell testified that he had extensively discussed the Machius ’95 reference with Dr. Borchert during the ’031 Patent prosecution. (Garbell, Tr. at 440:7-9, A-5671 and 16-19, A-5671, 441:9-10, A-5672.) He participated in the interference proceeding in which Machius ’95 figured prominently, and in which Dr. Borchert gave written and oral testimony regarding Machius ’95. (*Id.*) (FF 86-92; CL 91-92.)

(b) *Machius ’95 was highly material*

Machius ’95 was not cumulative to Suzuki. At a minimum, Machius ’95 provides highly relevant information not found in Suzuki and provides more motivation for a protein engineer to make the 179-180 deletion in BSG than the motivation provided by Suzuki, and provides a greater expectation of success. (Machius, Tr. at 774:3-22, A-6562.) Dr. Borchert himself admitted that there was information provided by Machius ’95 that was not found in Suzuki, such

¹³ See Appendix B for a detailed timeline of Novozymes’ experience with Machius ’95.

as the teaching that Suzuki's Region I (including the 179-180 deletion) is in an exposed surface loop. (Borchert, Tr. at 357:22-358:7, A-5588-5589, 359:12-360:7, A-5590-5591.) Mr. Garbell's admission that the '031 Patent might not have issued had Machius '95 been disclosed, is virtually dispositive of its materiality. (Garbell, Tr. 445:9-15, A-5676.) (FF 68-79; CL 90.)

(c) *Dr. Borchert and Mr. Garbell knew of the materiality of Machius '95*

Mr. Garbell testified that he had made the connection between the disclosure in Machius '95 of the Suzuki reference and the '031 Patent application. (Garbell, Tr. at 440:23-441:2, A-5671-5672.) Thus, Mr. Garbell was aware that the Machius '95 reference was relevant to the claims of the '031 Patent.

Given Dr. Borchert's extensive familiarity with and multiple citations to the Machius '95 reference, having been alerted by Mr. Garbell that Machius '95 summarizes Suzuki (Garbell, Tr. at 440:23-441:2, A-5671-5672), and given his admissions that Machius '95 adds to the teachings of Suzuki, Dr. Borchert knew or must have known of the materiality of Machius '95 to the '031 Patent application. It is hard to imagine Dr. Borchert not considering Machius '95 as relevant to the '031 Patent prosecution when he gave a declaration and was then deposed on Machius '95 at the same time the "option" plan was coming to fruition, in the September 2004 Examiner interview. (FF 93; CL 91-92.)

(d) *Dr. Borchert and Mr. Garbell breached their duty of candor to the PTO by intentionally withholding Machius '95*

Dr. Borchert, an inventor of the '031 Patent, was present at the interview with the Examiner, and was involved in developing the prosecution strategy for the '031 Patent. Mr. Garbell was the attorney who prosecuted the '031 Patent and executed the strategy. Thus, both Dr. Borchert and Mr. Garbell were involved with the prosecution of the '031 Patent and owed a duty of candor to the PTO. (CL 88.)

Novozymes concealed the highly material Machius '95 while prosecuting the '031 Patent. The only question is whether it did so with deceptive intent. It did.

Mr. Garbell admitted that if Novozymes had disclosed Machius '95 to the Examiner there was a possibility the '031 Patent would not have issued. (Garbell, Tr. at 445:9-14, A-5676.) And, Mr. Garbell was well aware of the "when in doubt" rule concerning disclosure of material information while prosecuting the '031 Patent. (Garbell, Tr. at 431:19-432:5, A-5662-5663, 444:23-445:14, A-5675-5676.) Remarkably, despite his extensive dealings with Machius '95 as well as his recognition that it at least summarizes Suzuki (Garbell, Tr. at 440:23-441:2, A-5671-5672), Mr. Garbell stated at trial that he did not make any affirmative decision about citing or not citing Machius '95. (Garbell, Tr. at 442:5-21, A-5673.) (FF 92-98; CL 88-95.)

Dr. Borchert admitted that Machius '95 contained teachings both including and beyond those of Suzuki (Borchert, Tr. at 357:22-358:7, A-5588-5589, 359:12-360:7, A-5590-5591). It is hard to imagine this as anything other than a concession of relevance and materiality. Yet, incredibly, Dr. Borchert argues that Machius '95 is immaterial to the '031 Patent. (Borchert, Tr. at 414:24-415:4, A-5645-5646.) (FF 75-76.)

Deceptive intent is rarely shown by direct evidence, but may be inferred from the totality of the evidence. *See Molins PLC*, 48 F.3d at 1180-91. Thus, the determination of deceptive intent involves a determination of whether Mr. Garbell and Dr. Borchert's explanations about their decision not to cite Machius '95 are credible. *See Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1582 (Fed. Cir. 1996). They are not. (CL 85-87.)

Mr. Garbell protests too much when he claims not to have even considered whether to disclose Machius '95. He and Dr. Borchert knew Machius '95 intimately and were litigating it in the interference precisely when carrying out their "option" plan. Novozymes made a decision not to disclose Machius '95, and made that decision for a reason—to assure that the '031 Patent would issue.

The evidence overwhelmingly shows that by withholding Machius '95, Novozymes was able to avoid an obviousness rejection on new grounds, which would have resulted, at the least, in delaying Novozymes' ability to secure patent coverage that would enable it to try to remove

SPEZYME® Ethyl from the marketplace, if not thwarting those plans altogether. Certainly, citing Machius '95 would have presented Novozymes with new, uncertain obstacles in its plan to secure patent coverage of the Suzuki deletion in BSG at "full speed." (Borchert, Tr. at 377:24-378:25, A-5608-5609; TE 516, A-8901-8902.) Fully cognizant that citing Machius '95 might have prevented it from obtaining a patent on BSG with a deletion in the "two expected/feared amino acids" (Borchert, Tr. at 377:11-378:23, A-5608-5609; TE 516, A-8901-8902), Novozymes' claims that it did not occur to Mr. Garbell to cite Machius '95, and that Dr. Borchert found Machius '95 to be immaterial, are simply not credible. The evidence gives rise to a compelling inference of deceptive intent.¹⁴ (CL 85-87, 94-95, 108.)

C. Inequitable Conduct Based on Misrepresentations in and Regarding the Borchert Declaration and Underlying Experiments

Driven by the success of SPEZYME® Ethyl to obtain a patent that would knock Genencor's product off the market, Novozymes also submitted the Borchert Declaration to the PTO. As a direct result of Novozymes' affirmative representations regarding the "unexpected" nature of the results, the PTO allowed the '031 Patent. In her reasons for allowance, Examiner Prouty said that the Borchert Declaration "establishes that the claimed variants exhibit unexpectedly large increases in thermostability when compared to the increase in thermostability obtained for the corresponding mutations taught by Suzuki *et al.*" (TE 101 at 756, A-7796.)

The '031 Patent would have not issued without Novozymes' affirmative representations regarding the nature of the results underlying the Borchert Declaration. Those representations were misleading, and were made with the intent of inducing the Examiner into helping

¹⁴ A claim may be patentable over a reference under the standards of novelty and nonobviousness, and yet be unenforceable because of the failure of the applicant to disclose that same reference to the PTO. *See Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1420-21 (Fed. Cir. 1989); *Gardco Mfg., Inc. v. Herst Lighting Co.*, 820 F.2d 1209, 1213 (Fed. Cir. 1987) ("a patent may be valid and yet be rendered unenforceable for misuse or inequitable conduct"). Thus, even *assuming arguendo*, that this Court finds the '031 Patent to be valid over Machius '95, the high degree of materiality and Novozymes' intent compel a conclusion that Novozymes committed inequitable conduct in procuring the '031 Patent by withholding Machius '95 during its prosecution, rendering the '031 Patent unenforceable.

Novozymes compete in the courtroom (because it was losing the battle in the marketplace). (FF 45-48; CL 96.)

(a) *Mr. Garbell and Dr. Borchert owed a duty of candor and had the motive to breach that duty*

Dr. Borchert and Mr. Garbell played key roles in Novozymes' efforts to obtain the '031 Patent. They drove the "Option 1/Option 2" planning, and presented the alleged "unexpected" results to the Examiner, knowing that they were irrelevant to the only rejection actually pending at the time. Going into the interview with Examiner Prouty, Dr. Borchert was well aware that if claims were going to issue, they would do so only on the basis of his declaration, and that such claims were going to be asserted against Genencor (Borchert, Tr. at 397:12-18, A-5628), whom he perceived to be Novozymes' "main competitor." (Borchert, Tr. at 355:8-356:15, A-5586-5587.) In fact, Mr. Garbell told Dr. Borchert that a showing of "unexpected results" was Novozymes' only hope for procuring a patent on a BSG from which amino acids 179 and 180 were deleted. (TE 110 at NV-0200006, A-8170.) (FF 30-40, 45-48, 104-106; CL 98-108.)

(b) *Novozymes' misrepresentations*

Despite being told that any results he obtained in the course of his experiment, whether good or bad, would have to be disclosed to the PTO (Garbell, Tr. at 431:13-18, A-5662), Dr. Borchert resorted to manipulation and non-disclosure of experimental conditions and data to ensure that a declaration purporting to present evidence of "very surprising" and "unexpected" results would be submitted to the PTO. (FF 39-40; CL 98, 102.)

- *Novozymes misrepresented the comparison vs. Suzuki.* Dr. Borchert had studied Suzuki in great detail (Borchert, Tr. at 351:14-16, A-5582), and thus must have been aware of how the conditions under which the experiment underlying his declaration differed from those of Suzuki, including not preheating the buffer, using 80°C (instead of Suzuki's 90°C) and using a calcium concentration that was 100-fold less than that of Suzuki. Neither during his interview with Examiner Prouty nor in the Borchert Declaration, did

Dr. Borchert make the Examiner aware of the differences between his conditions and the Suzuki conditions, or of the consequences of the differences in these conditions. (Borchert, Tr. at 382:4-11, A-5613, 396:18-397:7, A-5627-5628.) (FF 104-106, 110; CL 99.)

- *Novozymes misrepresented the half-life of BAN WT.* Dr. Borchert knew or must have known that the conditions employed in his thermostability experiment would have resulted in an unreliable half-life for BAN WT that was greatly inflated due to the ramp-up period. (Klibanov, Tr. at 525:6-526:8, A-5756-5757; Borchert, Tr. at 26:17-22, A-5026.) (FF 108-115; CL 99.)
- *Novozymes misrepresented the “unexpected” nature of the results.* Dr. Borchert testified that one of ordinary skill in the art could not have had a specific expectation of the increase in thermostability in BSG relative to the increase in thermostability of BAN upon introduction of that same deletion. (Borchert, Tr. at 410:15-19, A-5641.) Even so, Dr. Borchert and Mr. Garbell asserted to the PTO that the magnitude of the increase in stability of BSG del over BSG relative to the increase in stability of BAN del over BAN was “very surprising” and “significantly” and “substantially” greater than what would have been expected. (TE 101 at 696-697, A-7736-7737; TE 508 at ¶ 9, A-8861.) (FF 132-134; CL 101-103.)
- *Novozymes omitted critical data points.* Dr. Borchert knew that the Borchert Declaration did not contain the data points measured for BSG del at 2881 minutes and at 2940 minutes. (Borchert, Tr. at 396:16-17, A-5627.) Dr. Borchert testified that “we deliberately decided not to include the measurements in the final data” submitted to the PTO (Borchert, Tr. at 386:18-19, A-5617), and never brought up these omissions during the interview with the Examiner. (Borchert, Tr. at 386:20-22, A-5617.) Nor did Mr. Garbell, who failed in his duty to assure that only objective, reliable evidence was

represented to the Examiner, because he never even asked Dr. Borchert about how the data had been obtained, or whether it was all presented in the Declaration. (*Cf.* MPEP § 716.02(b), *et. seq.*) (FF 121-131; CL 100.)

- *Novozymes misrepresented the half-life of BSG del.* From the calculation, Novozymes presented the Examiner with an extrapolated half-life for BSG del, even though there was no evidence to justify the extrapolation. (FF 116-120; CL 101.)

In the end, nothing about the Borchert Declaration was reliable or fairly presented. The only questions are whether Novozymes' misrepresentations to and about Borchert Declaration were material and whether Novozymes had the required "deceptive intent." The answers are clear: yes.

(c) *Misrepresentations in and omissions from the Borchert Declaration were material*

In this case, the materiality of the Borchert Declaration is self-evident. Novozymes based its argument for patentability on allegedly "unexpected results" presented expressly in comparison to the results shown in Suzuki. This "comparison" to the improvement in thermostability shown in Suzuki was no comparison at all, given the many differences between the Borchert "experiment" and Suzuki's work.

These differences were core to Novozymes' misrepresentations. Novozymes chose the "fight," using the "option" plan to gain time to put together an experiment Novozymes told the Examiner showed unexpected results compared to what was shown in Suzuki. Novozymes used experimental conditions that varied from Suzuki in ways that helped its case, and never identified those differences or explained their significance as required in MPEP §§ 716.02 (b), (e). (CL 54.)

Novozymes also manipulated the resulting data, to give the Examiner the impression that the Suzuki deletion in BSG gives a 5.7-fold greater improvement in thermostability than the corresponding deletion in BAN, rather than the more modest less than two-fold differential Dr. Klibanov calculated when he took the ramp-up effect into account. (Klibanov, Tr. at 549:7-8,

A-5780, 610: 3-11, A-6018.) Novozymes' selection of conditions different from Suzuki for the experiment underlying the Borchert Declaration and its manipulation of the data were designed to convince the Examiner of the existence of "unexpected" results, despite Dr. Borchert's own admission that he had no expectation regarding the magnitude of the results. (Borchert, Tr. at 410:10-19, A-5641.) (FF 132-134; CL 101-102.)

There is no question that the Examiner relied on the alleged results as the sole reason for allowing the '031 Patent to issue. The Examiner even stated in the Notice of Allowability that although Novozymes' claims were *prima facie* obvious over Suzuki and the Bisgard-Frantzen PCT, the Borchert Declaration "establishes that the claimed variants exhibit unexpectedly large increases in thermostability when compared to the increase in thermostability obtained for the corresponding mutations taught by Suzuki *et al.*" (TE 101 at 756, A-7796.) (FF 48; CL 96, 101-102.) Novozymes' misrepresentations were legally material to the '031 Patent prosecution.

(d) *Novozymes Acted With Deceptive Intent*

Dr. Borchert and Mr. Garbell have not admitted deceptive intent, nor need they do so for the Court to find they acted inequitably. "Intent need not be proven by direct evidence; it is most often proven by a showing of acts, the natural consequences of which are presumably intended by the actor." *Molins PLC*, 48 F.3d at 1180. (CL 85-87.) Here, the evidence overwhelmingly shows that Dr. Borchert and Mr. Garbell were aware of their acts regarding the declaration, and intended their natural consequences—the speedy issuance of the '031 Patent.

Just as he knew that a showing of unexpected results was crucial to the issuance of the '031 Patent (Borchert, Tr. at 354:22-355:4, A-5585-5586; TE 110 at NV-0200006, A-8170), Dr. Borchert knew that the conditions he selected for the "experiment" were significantly different from Suzuki's conditions and would distort the magnitude of the thermostabilization of BSG relative to BAN upon introduction of the Suzuki deletion. Dr. Borchert never identified and explained these differences (in temperature, in calcium concentration, in pre-heating), "relying"

on the overworked Examiner to make a detailed comparison of the Borchert Declaration and Suzuki and then guess at the significance of the differences that she could find. (CL 102.)

The final misrepresentation was the most often repeated—yet, the results were not unexpected. Dr. Borchert admitted that he had no expectation about the magnitude of thermostabilization in BSG prior to performing his experiment. (Borchert, Tr. at 410:10-19, A-5641.) (FF 132.) Yet, Dr. Borchert and Mr. Garbell continued to assert to the PTO in the amendment of September 6, 2004 and the Borchert Declaration that Novozymes results were “very surprising” and “unexpected.” (FF 46.)

The only reasonable conclusion based on the totality of the evidence (including the non-disclosure of Machius ’95) is that Dr. Borchert and Mr. Garbell engaged in a systematic pattern of hiding material information from or misrepresenting it to the Examiner, with the purpose of deceiving the PTO into issuing the ’031 Patent and facilitating the hoped-for removal of SPEZYME® Ethyl from the market. That pattern of misrepresentation, itself so convincing of Novozymes’ deceptive intent,¹⁵ continued to the very end of the ’031 prosecution. Novozymes’ Mr. Garbell made much at trial of the fact that the Examiner cited Machius ’95 in a related prosecution, after the ’031 Patent was allowed but not issued. In response, Novozymes did ... nothing. It did not pull the ’031 Patent from issuance or do anything to address the problems its non-disclosures created. Novozymes’ failure even to attempt any “cure” further evidences its deceptive intent. *Cf. eSpeed*, 2006 WL 416860, at *7. (CL 108-109.)

It is instructive to compare this case to *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963 (Fed. Cir. 2006). There, a patentee had withheld from the Patent Office data obtained from comparative testing results but later presented that data to the Examiner; the Federal Circuit noted that there was evidence from which the trial court could have found an intent to deceive, but

¹⁵ In *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, the Federal Circuit upheld a district court’s finding that the patentee’s “persistent course of material misrepresentations, omissions, and half-truths to the PTO” amounted to clear and convincing evidence of deceptive intent. *PerSeptive Biosystems*, 225 F.3d at 1320. (CL 86.)

chose not to disturb the trial court's finding that the ultimate submission to the Examiner of the previously withheld data deflected a finding of deceptive intent. *Id.* at 972. In stark contrast, Novozymes failed to make any effort to "cure" its nondisclosures and misleading presentation to the Examiner, even though Novozymes' Mr. Garbell admitted that the '031 Patent might not have issued had Machius '95, at least, been disclosed to the Examiner. The conclusion is inescapable – Novozymes acted with deceptive intent. (CL 84-87, 102.)

The required "balancing test" is easily met here. *See Purdue Pharma*, 438 F. 3d at 1128-29. Withholding Machius '95 and misrepresenting the conditions, results and meaning of the Borchert Declaration were highly material to the '031 Prosecution, so little evidence of intent is required. Yet, the evidence of Novozymes' deceptive intent is clear, convincing, substantial and compelling. The '031 Patent issued as the result of inequitable conduct.

Genencor is entitled to judgment that the '031 Patent is unenforceable.¹⁶ (CL 111.)

¹⁶ Novozymes' inequitable conduct has two other consequences. First, the finding that Novozymes is guilty of inequitable conduct demonstrates that this is an "exceptional case"; Genencor is entitled to its attorneys' fees of this meritless case. *See* 35 U.S.C. § 285; *Phonometrics, Inc. v. Westin Hotel Co.*, 350 F.3d 1242, 1245 (Fed. Cir. 2003); *A.B. Chance Co. v. RTE Corp.*, 854 F.2d 1307, 1312 (Fed. Cir. 1988). (CL 115-122.) Second, Novozymes' inequitable, fraudulent actions are sufficiently egregious such that, combined with Novozymes' plan to delay prosecution and obtain broader claims, the '031 Patent is also unenforceable due to prosecution laches. (CL 112-114.)

VI. **CONCLUSION**

Genencor and EDC are entitled to judgment as set forth in their proposed Conclusions of Law, p. 93.

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